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Lectures

Selected Lectures of the 13th International Workshop on Neonatology

THE POWER OF EPIGENETICS TWINS: IDENTICAL BUT DIFFERENT

CAGLIARI (ITALY) • OCTOBER 25TH-28TH, 2017

The Workshop has been organized with the patronage of the Italian Society of Neonatology (SIN), the Italian Society of Pediatrics (SIP), the Italian DOHaD (Developmental Origins of Health and Disease) Society, the Italian Society of Preventive and Social Pediatrics (SIPPS), the Union of European Neonatal and Perinatal Societies (UENPS), the International Federation of Clinical Chemistry and Laboratory Medicine (IFCC), the Union of Middle-Eastern and Mediterranean Pediatric Societies (UMEMPS), the European Association of Perinatal Medicine (EAPM) and lastly the Italian-Romanian Society of Pediatrics.

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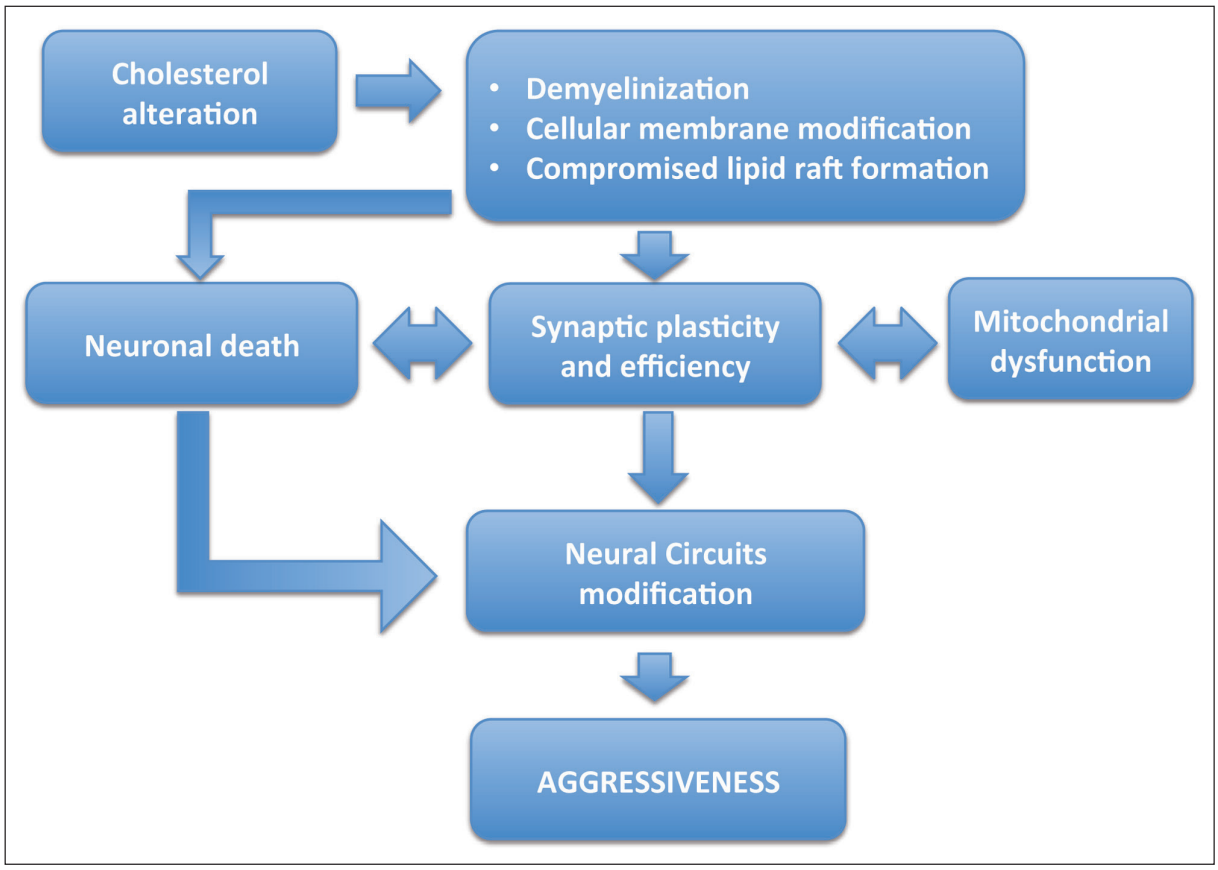

Figure 1 (LECT 71). Potential biological mechanism of aggressive behavior.

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LECT 72

DOHaD, NUTRITION AND BASIC RESEARCH

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The "DOHaD" (Developmental Origin of Health and Disease) theory describes how *in utero* exposure to environmental factors may have long-term effects on the structural and functional development of the fetus. Extensive retrospective studies, such as those on the Dutch famine of 1944, have reported correlations between maternal diet or nutritional status and the risk of pregnancy pathologies or to develop adverse conditions in the future adult. Indeed, macro- and micronutrients taken with the maternal diet can regulate the stability and expression of fetal/placental DNA and phenotype adaptations through epigenetic modifications, reversible mechanisms that occur without changes in the DNA sequence (DNA methylation, histone acetylation, microRNA) [1]. Recently, a large prospective longitudinal cohort study in humans (MANOE study) reported that maternal intake of methyl donors, especially during the periconceptional period, can affect the epigenoma of the offspring in genes related to obesity and diabetes. However, many observations on this issue are born from basic research studies performed on the placenta: placental epigenetic modifications are one of the main mechanisms through which nutritional and environmental factors affect fetal growth. Epigenetic regulation of placental phenotype and function has been extensively studied in the mouse. For example, "imprinted" placental genes (IGF2, H19) act as "nutritional sensors" by varying their methylation status based on environmental conditions. In our lab, we have recently reported lower functionality in the placenta of overweight/obese women with high gestational weight gain, with an important role in fetal sex [2]. Those placentas also exhibit alterations

in mitochondrial content suggesting a bioenergetic placental imbalance resulting from an altered nutritional intake. Methylation of mitochondrial DNA may also be involved in these mechanisms [3]. Future research will allow to fully understand the underlying mechanisms of pregnancy pathologies in relation to maternal-fetal nutrition.

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LECT 73

ENVIRONMENTAL FACTORS AND EPIGENETIC MECHANISMS

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Epigenetic mechanisms (DNA methylation, histone tail modification and chromatin remodeling, ncRNA interventions) contribute to gene expression regulation. Several environmental exposures, in particular to endocrine disruptors, are able to interact with genetic susceptibility factors, by interfering with our epigenome, increasing the occurrence of complex diseases such as obesity, behavioural disorders and other pathological conditions. The first stages of development of an organism represent a particularly sensitive period, as well as childhood and adolescence. The entire differentiation process that characterizes intrauterine development is the result of a complex series of cell-specific epigenetic events, including "reprogramming" of specific epigenetic patterns of DNA methylation in each individual cell. There are therefore a number of crucial windows in the early stages of embryonic development during which the epigenetic mechanisms responsible for differentiation are particularly sensitive to influences by environmental factors. Some of the environmental exposures that are likely to have a greater impact on epigenetic mechanisms will be considered. The most studied are exposures to heavy metals, particularly arsenic, to endocrine disrupters, including obesogens, diet and some lifestyle, including alcohol, some pharmacological treatments, and stress. Complex diseases with an epigenetic etiology can be prevented through primary prevention actions, moreover it has been seen a great potentiality in therapeutical interventions.

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LECT 74

PERINATAL PROGRAMMING AND BRAIN

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The Developmental Origins of Health and Diseases theory that states that the health state of a human being is determined during pregnancy meaning that "what happens in pregnancy does not stay in pregnancy" but it will affect the entire life course. This is particularly true when we focus our attention at the brain, according to recent literature. Furthermore, this organ complete its development in the first years of life, thus investigators are studying any possible epigenetic factor that could modify, alter or disrupt this process. First of all, maternal factors such as diet, lifestyles and drugs assumption are of primary importance [1]. According to recent studies, other than in case of malnourishment that can result in low weight at birth or several deficiencies of nutrients that are fundamental for an appropriate brain development; even children born from obese mothers can display alterations in brain maturation (high levels of glucose seem to be "toxic" and possible vitamin D deficit) that could lead to behavioral disturbances. For what concerns lifestyle, leaving aside substances abuse, smoking during lactation and gestation is associated with serious brain malformations with several regions to be hypotrophic. Even drinking is related to brain abnormalities (Fetal Alchool Syndrome, FAS): it literally kills the neurons giving rise to phenomena such as apoptosis and autophagy among others, at least from evidence coming from animal studies.